REMARKS

Claim Status

Claims 1, 3, 5-8, and 11-45 are pending in the present Application. Claims 13-15 and 24-45 are withdrawn from consideration. Claims 2, 4, 9, and 10 have been canceled without prejudice. Claims 1, 3, 5, 6-8, 11, 12 and 16-23 are rejected.

Claim 5 has been amended to correct Claim dependency. Claim 22 has been amended to clearly recite the kit element of instructions provided to a user. Support for the amendment is found in Original Claim 22.

No new matter has been added. Thus, entry and consideration of the amendments is respectfully requested.

REJECTIONS

Rejection Under 35 USC § 112, 2nd Paragraph

Claims 5, 22 and 23 are rejected under 35 USC § 112, 2nd Paragraph as being indefinite for allegedly failing to point out and distinctly claim the subject matter which the Applicant regards as his invention.

Claim 5 is rejected as being indefinite because it is based on a rejected claim; thus the Examiner asserts that the metes and bounds of the Claim can not be determined.

The Applicants respectfully traverse the rejection. The dependency of Claim 5 has been corrected such that Claim 5 depends from Claim 1. Therefore, the Applicants assert that Claim 5, as amended, is not dependent from a Claim rejected under § 112, 2nd Paragraph, and that the rejection has been obviated. The Applicants respectfully request withdrawal of the rejection.

Claims 22 and 23

The Examiner alleges that the elements in the Claim 22 do not recite any structural limitations or concrete elements; rather the Examiner alleges they recite unspecified

systems for performing steps in the claimed method. Addtionally, the Examiner alleges that the interrelationship between the two systems is a computational step, determination of a ratio, and not a recitation of how the two components are related. Claim 23 is rejected as dependent on Claim 22.

The Applicants respectfully traverse the rejection.

Claim 22 does specify two elements: A kit comprising *inter alia a first measuring element or system* for measuring the level of at least one anti-inflammatory cytokine in a biological sample from a mammalian subject before treatment and at at least one time point after or during treatment, *a second measuring element or system* for measuring the level of at least one pro-inflammatory cytokine in a biological sample from said mammalian subject before treatment, and at at least one time point after or during treatment, and usage instructions…

The kits are described beginning at page 12, line 5 of the specification. Example structure and measuring elements or systems are described in the specification, starting at page 12, line 13, wherein it is stated that: "Such measuring elements or systems may include those known to one skilled in art, non-limiting examples of which include immunosorbent assays, enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), multiplexed ELISAs on microarray platforms, multiplexed ELISAs using coded microspheres coupled with a flow cytometer detection systems, bioassays, Western blots, chromatograph-based separation systems, RT-PCR, competitive reverse transcription PCR, Northern blots, gene arrays, direct measurement of m-RNA, and mixtures thereof,…". Therefore, the Applicants assert that Claim 22 does specify two concrete elements or systems as such terms are defined in the Specification.

Furthermore, the Applicants submit that Claim 22 does specify the interrelationship between the two measuring elements or systems. Claim 22, as amended, recites the structural element of instructions provided to a user. Both measuring elements or systems measure cytokines. One system measures anti-inflammatory cytokines and the other system measures pro-inflammatory cytokines. The instructions relate the two measuring

elements or systems. The Applicants therefore submit that Claim 22, as amended, does recite how the two systems are related.

Therefore, the Applicants assert that the rejection has been overcome and respectfully request withdrawal of the rejection with respect to Claims 22 and 23.

Rejection Under 35 USC § 112, 1st Paragraph

Claims 1, 3, 5-8, 11, 12 and 16-21 are rejected under 35 USC § 112, 1st Paragraph for allegedly failing to comply with the enablement requirement.

The Examiner asserts that only methods which measure cytokine levels in tissues directly from the bowel region, or methods which measure cytokine production by peripheral blood mononuclear cells with *in vitro* stimulation, gut lymphoid tissues with *in vitro* stimulation, or gut lymphoid tissues without *in vitro* stimulation are enabled.

Additionally, the Examiner asserts that the working examples teach only measurement of ratios of anti-inflammatory to pro-inflammatory cytokines in IBS patients' PMBC's upon probiotic *in vitro* stimulation, and that there are no teachings of measurement of ratios of anti-inflammatory to pro-inflammatory cytokines in IBS patients' PMBC without probiotic *in vitro* stimulation. The Examiner asserts that one of skill in the art would not predict that measurement of changes of ratios of anti-inflammatory to pro-inflammatory cytokines in IBS patients' PMBC without probiotic *in vitro* stimulation would be indicative of changes in patients' disease or condition or efficacy of treatment.

The Applicants respectfully traverse the rejection. At page 14 of the Specification, lines 17-20 it is described that PMBCs from IBS patients (treated with *Bifidobacterium infantis* 35624) were cultured either alone in medium (*no stimulation)* or with 0.1μg/ml *E. coli* 0111B4 lipopolysaccharide, 1μg/ml phytohemagglutinin or 10^7 CFU/ml whole *Bifidobacterium infantis* 35624 for 3 days. Table 1 shows use of non-stimulated PMBCs. In addition, Figures 4, 5, and 6 show that the ratio of anti- and pro-inflammatory cytokines produced by gut-derived cell types *in vitro* following stimulation with probiotic bacteria is greater than the same ratio produced by non-stimulated control samples or

samples stimulated with pathogenic bacteria. Therefore, the Applicants submit that the Specification does indeed teach measurement of ratios of anti- to pro-inflammatory cytokines in IBS patients' PMBC without probiotic *in vitro* stimulation, which ratios can be used as controls and compared to the ratios of PMBCs with probiotic stimulation for evaluation of changes in patients' disease or conditions or efficacy of a tratement. Therefore, the Applicants assert that the rejection has been overcome.

Additionally, the Examiner asserts that administration of IL-10 or antibodies to pro-inflammatory cytokines are art-recognized methods of treating IBD. The Examiner asserts that such treatments would result in increasing IL-10 levels and/or decreasing pro-inflammatory cytokine levels which would change the ratios of levels of IL10 to IL-12 etc. but that one could not determine if such changes would be indicative of efficacy of treatment or are a result of the administration of therapeutic compound, and that there are no teachings in the disclosure to enable the skilled practitioner to differentiate between these possibilities without undue experimentation.

The Applicants respectfully traverse the rejections. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. See MPEP § 2164.01 citing *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ 2d 1217, 1223 Fed. Cir. 1988. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. See MPEP § 2164.01 citing *In re Certain Limited-Charge Cell Culture Microcarriers* 221 USPQ 1165, 1174, Int'l Trade Comm'n 1983, *aff'd. sub nom., Massachusetts Institute of Technology v. A.V. Fortia,* 774 F.2d 1104, 227 USPQ 428 Fed. Cir. 1985.

As previously noted by the Examiner, the factors to be considered to determine whether experimentation is "undue" include the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a).

The Applicants assert that undue experimentation would not be required by one of skill in the art in order to practice the invention, and that the Claims are enabled. The Applicants provide sufficient background for one of skill in the art to understand the problems associated with inflammatory bowel diseases, and the methods and technologies described in the present Specification. In addition, the level of skill of one in the art would be relatively high as the invention involves scientific and medical principles. Furthermore, complex experimentation is common to the biological and medicinal arts.

Even though such treatments may be known, and the subject's response might be due to the administration of an anti-inflammatory cytokine (which would raise the level of anti-inflammatory cytokine) or antibody to a pro-inflammatory cytokine (which would lower the levels of pro-inflammatory cytokine) the methods of the Application, and studying changes in ratios of cytokines can be used to study the subject's response to the treatment, and to determine the effect of the treatment, without undue expermentation. For example one could determine the ratio of anti- to pro-inflammatory cytokine and study and observe the treated patient to correlate the ratio to effectiveness of treatment. See Table 1 and the explanation of Table 1 at page 15, lines 12-16 which describe the negative correlation between the change in abdominal pain/discomfort and the change in IL-10 to IL-12 ratio, which indicated that the change in ratio was associated with relief from the IBS symptom of abdominal pain/discomfort. Thus, one could use the ratios to study effectiveness of treatment (correlating ratios and symptoms) and show that the change in ratio is not simply due to the administration of a treatment, but rather the effectiveness of a treatment. Therefore, the Applicants assert that the rejection has been overcome.

The Applicants therefore assert that the Claims 1, 3, 5-8, 11, 12 and 16-21 are enabled and that the rejections have been overcome. Thus, the Applicants respectfully request withdrawal of the rejections.

Rejections Under 35 USC § 102

Claim 22 is rejected under 35 USC § 102(b) as allegedly being anticipated by Vignali, 2000 Journal of Immunological Methods 243:243-255 (hereafter "Vignali").

The Examiner asserts that Claim 22, given its broadest reasonable interpretation, is drawn to a kit for measuring cytokines in a biological sample from a mammalian subject. The Examiner asserts that there are no structural limitations recited as to the contents of the kit and that the Claim is not directed to a method, so the intended use of the kit and a recitation of when the measurements are to be performed is not given patentable weight.

The Examiner asserts that the Claim does not explicitly recite any structural element or components and thus that art which teaches components to be used for measurement of the recited cytokines will anticipate the limitations of the Claim.

The Examiner asserts that Vignali teaches a FlowMetrix™ system quantifying the concentration of 15 cytokines simultaneousoy in a 100 microliter sample. Some of the cytokines are among the cytokines recited in the present Claims. The Examiner asserts that once the concentrations of cytokines are determined, ratios between them may be easily determined and the skilled artisan may then draw conclusions. In addition, the Examiner asserts that the FlowMetrix™ system is soled by Invitrogen and that on the company's website it is stated that kits are available. Therefore the Examiner asserts that Vignali anticipates the Claim.

The Applicants respectfully traverse the rejection. Under 35 USC §102, anticipation requires that all the Claim elements appear in a single prior art document. "A Claim is anticipated only if each and every element set forth in the Claim is found, either expressly or inherently described, in a single prior art reference." MPEP § 2131 citing *Verdegal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2D 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as contained in the … Claim." MEPE § 2131 citing *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2D 1913, 1920 (Fed. Cir. 1989).

Vignali discloses that the simultaneous detection of various analytes can be achieved using the FlowMetrix™ assay. Vignali discloses that multiple cytokine levels can be measured simultaneously. Vignali is simple a research paper that traces the historical

association between microspheres and flow cytometry, the development of particle-based flow cytometric assays, how they compare with current assays and potential future developments. Because various kits to measure various analytes may be available via a website does not teach every element of the Claim. The Applicants maintain that Vignali does not disclose a kit for measuring the particular cytokines recited in Claim 22, in a supernatant from cells cultured from a biological sample. Vignali simply discusses assay methods that can be used to measure various analytes and discusses the advantages and disadvantages of various assay methods and devices.

Therefore, because all elements of the Claim are not found in Vignali, Vignali can not, as a matter of law, anticipate the Claim. The Applicants, therefore, respectfully request that the rejection be withdrawn.

Rejections Under 35 USC § 103

Vignali

Claim 23 is rejected under 35 USC § 103(a) as being allegedly unpatentable over Vignali.

The Examiner acknowledges that Vignali does not disclose a kit comprising means for collecting biological samples. However, the Examiner asserts that the Claims do not recite any specific component or element for obtaining biological samples. Therefore, the Examiner asserts that any instrument would meet the limitation of a 'means for obtaining said biological samples'. The Examiner asserts that the system used by Vignali is sold as a kit to measure cytokines, via Vignali's disclosure of the FlowMetrix assay. The Examiner characterizes the FlowMetrix assay as a kit, and asserts that one of skill in the art would understand that a sample must be obtained, and that therefore one of ordinary skill in the art would be motivated to include an instrument or sampling device.

The Applicants respectfully traverse the rejection. The Examiner has not established a *prima facie* case of obviousness, even in light of *KSR International Co. v. Teleflex Inc.* 82 USPQ2d 1385 (U.S. 2007) ("KSR"). See also MPEP § 2143.01. KSR did not eliminate the need for at least some suggestion, motivation, or expectation of success for making a given modification. A *prima facie* case of obviousness has not been established because

the cited document does not teach or suggest all of the claim limitations of Claim 23, or provide any reasonable motivation or expectation of success for trying the presently claimed invention. See MPEP § 2143.03.

The Examiner maintains that Vignali discloses a kit for measuring cytokines in a biological sample. As argued above, Vignali does not disclose a kit, nor particularly, the kit as claimed. Vignali only discloses various assay methods and devices, and compares them. Thus, there is no suggestion, motivation or expectation to create or provide any particular kit. Vignali simply discusses research methods, one of which is the FlowMetrix assay, which is also not a kit. Thus, because there is no motivation initially to create or provide a kit, from disclosure and survey of various assay methods, there is no motivation to add to such a kit a means for collecting biological samples. Even if one of skill in the art understood that a biological sample would need to be obtained, such information would not have led one of skill in the art to the present invention. Vignali simply performs various assays on various equipment to test the limits, practicality, cost, advantages and disadvantages of various assays done on various equipment. Vignali does not suggest combining systems for measuring cytokines, and instructions for use of the systems and calculation of cytokine ratios into a kit or provide motivation or expectation of success for creating a kit. Thus, there is no expectation of success found in Vignali for creating a kit containing a means for collecting biological samples.

Therefore, Vignali does not provide the requisite motivation, predictability or expectation of success to have led one of ordinary skill in the art to the present invention, even in light of *KSR*. Thus, the Applicants assert that the rejection has been overcome.

Towaga

Claims 1, 3, 5, 16, 17, 19, and 20 are rejected under 35 USC § 103(a) as being allegedly unpatentable over Towaga et al. 2002 Am J. Physiol, Gastrointestinal Liver Physiol 283:G187-G195 ("Towaga").

The Examiner asserts, that Towaga teaches an experimental rat model of IBS, that one group of rats is treated with a test compound and the second (control) group I streated

only with saline. The Examiner asserts that one of skill in the art would consider the control group to be the equivalent of a human patient before treatment. The Examiner further asserts that Towaga teaches changes in levels of anti- and pro-inflammatory cytokines as a result of treatment of IBS, and that these changes may be indicative of efficacy of treatment for IBS. The examiner asserts that one of skill in the art would consider the measurement of efficacy of treatment to be the equivalent of measuring changes in cytokine levels in human patients before and after treatment.

Additionally, the Examiner acknowledges that Towaga does not teach measuring cytokine levels before and after treatment *or* determining the ratios of cytokines before and after treatment. However, the Examiner asserts that it would have been obvious, in treating IBS patients, to measure cytokine levels in a biological sample before and after treatment to assess efficacy of treatment, and that one would have been motivated to make the modification beause Towaga suggests clinical experimentation to determine efficacy of the administration of lactoferrin for treatment of IBS, and that one of skill in the art would be motivated, (by cost and efficiency) to measure cytokine levels before treatment versus having a control, untreated group of patients. Lastly, the Examiner asserts that one would have been motivated to calculate ratios of anti- and pro-inflammatory cytokines as a way of determining shifts in patterns of cytokine levels, and that one would reasonably expect success because methods of measuring cytokine levels in biological samples is well known and taught by Towaga.

The Applicants respectfully traverse the rejection and maintain that the Examiner has made too great a leap. Towaga details only one particular experiment in rats using induced colitis. Towaga does not provide any suggestion or motivation to study 'before and after' results, or to set up such experiments, without controls. Towaga does not suggest studying ratios of cytokines to establish and analyze shifts in patterns of cytokine levels to evaluate efficacy of treatment. In particular, Towaga does not suggest or provide motivation for the particular cytokines and ratios as claimed. Towaga simply induces colitis in rats and compares cytokine levels to those of normal, control rats in conjunction with studying physical aspects of the induced disease such as thickness of the

colon, weight of the colon, and presence and size of lesions, in order to determine whether lactoferrin is effective against the induced colits.

The Applicants maintain that there is no suggestion, motivation or predictability to do *completely different* clinical experiments, with completely different protocols and subjects, or to use or analyze 'before and after' data in a clinical setting simply because such things could be able to be done. The Applicants assert that simply because one *could* do any variety of experiments on any compound in an animal or in a clinical setting and perform various analysis is not sufficient, even in light of *KSR*. There still must be some reason or motivation to jump from a rat study with a disease vs. control group, to choose a particular experiment, particular compounds to study, or particular analysis to perform. Towaga does not provide such motivation, particularly with the wide range of experiments possible in the fields of animal and human studies, and the vast range of analyses that could be performed when studying various disease conditions, various biological parameters, and various human and/or animal subjects. There is simply no suggestion in Towaga that would lead one skilled in the art of animal studies to make the jump to a very different human study.

Therefore, the Applicants submit that the disclosure of Towaga, even in combination with the knowledge of one skilled in the art does not suggest the claimed invention, and that one of skill in the art would not have been led to the claimed invention based on the disclosure of Towaga. Therefore, the Applicants assert that the rejection has been overcome.

Towaga in view of Vignali

Claims 18 and 21 are rejected under 35 USC § 103(a) as being allegedly unpatentable over Togawa as applied to Claims 1, 17 and 20 in view of Vignali.

The Examiner asserts that Towaga suggests clinical experimentation to determine efficacy of administration of lactoferrin as treatment for IBS, and that Towaga also discloses changes in levels of anti- and pro-inflammatory cytokines. The Examiner further asserts that the clinical researcher would be motivated to measure cytokine levels

before treatment instead of using a set of control animals because such is known practice in clinical research and is efficient and cost effective. The Examiner asserts that Towaga discloses measuring cytokine levels with ELISA assays, and that therefore it would have been obvious to modify the Towaga and substitute the multiplex assay taught by Vignali for the ELISA assay of Towaga. The Examiner asserts that one would have been motivated to do so, and anticipate success, because both method involve immunological methods of measuring cytokines, and Vignali teaches a more efficient method of quantifying the concentration of 15 cytokines simultaneously. Finally, the Examiner asserts that knowing the results of cytokine measurements, one would have been motivated to compute ratios as a way of quickly and efficiently determining shifts in patterns of cytokine levels.

The Applicants respectfully traverse the rejection. The Applicants maintain that one o skill in the art would not have been motivated to make the jump from one type of rat study to a different type of human study, simply because clinical study techniques are generally known, even if Towaga were combined together with Vignali and a FlowMetrix™ system were used. Simply because Vignali discloses a type of assay useful for measuring cytokines, and Towaga discloses a particular rat experiment in which cytokines were measured, does not disclose or suggest, or provide motivation or expectation of success for determining particular cytokines to measure and compare in humans, to use as a way to test and evaluate efficacy of treatments for IBS in humans. Perhaps one could analyze the cytokine levels of Towaga with such a system as disclosed in Vignali. However, one would not have arrived at the claimed method of determining the efficacy of a treatment of inflammatory diseases of the bowel in mammals *in vivo*. Towaga and Vignali together do not suggest or provide motivation or expectation of success for a clinical method, using samples from a biological subject, in which particular cytokine levels are determined and ratios analyzed, as claimed. The Applicants therefore assert that Towaga and Vignali taken together do not contemplate such a method as claimed.

Therefore, the Applicants assert that the rejection has been overcome. In addition, because Claims 18 and 21 depend ultimately from Claim 1 which the Applicants assert is

novel and non-obvious over the cited documents, the Applicants submit that Claims 18 and 21 are also novel and non-obvious over the cited documents.

Towaga in view of Blumberg

Claims 6-8 are rejected under 35 USC § 103(a) as being allegedly unpatentable over Togawa as applied to Claim 1 in view of Blumberg et al. 1999 Current Opinion in Immunology 11:648-656 ("Blumberg").

The Examiner asserts that Togawa teaches measurement of various cytokines, and that Blumberg notes the importance of the balance of particular cytokines in managing and assessing IBDs, and the Blumberg discloses that IL-12 is a key factor in the pathogenesis of the TNBS-induced colitis model of Towaga, and induces overproduction of IFN-γ and TNF. The Examiner also asserts that Blumberg teaches the importance of the balance (which the Examiner terms, ratio) between anti- and pro-inflammatory cytokines, and that both Towaga and Blumberg teach the importance of disturbed balance between anti- and pro-inflammatory cytokines in IBD.

Therefore, the Examiner asserts that it would have been obvious to modify the teachings of Togawa and substitute measurement of the pro-inflammatory cytokines taught by Blumberg for the pro-inflammatory cytokine taught by Towaga and the anti-inflammatory cytokine of Blumberg for the anti-inflammatory cytokine taught by Towaga. The Examiner asserts that one would have been motivated to measure changes in cytokine levels since Towaga teach changes in cytokine levels in response to therapeutic administration fo lactoferrin. The Examiner also asserts that calculation of ratios would have been obvious as a way of monitoring changes in the balance of levels of anti- and pro-inflammatory cytokines.

The Applicants respectfully traverse the rejection. As argued above, the Applicants maintain that Towaga does not suggest establishing or analyzing any ratios of cytokines, nor particularly the claimed ratios. Blumberg also does not suggest establishing or analyzing ratios of cytokines, nor the importance or utility thereof for testing or determining efficacy of a potential treatment. Blumberg simply notes that there is likely

an on-going balance between pro- and anti-inflammatory cytokines, and their release and activity in body systems in relation to inflammation. Blumberg is simply a review of known animal models of mucosal inflammation and their *potential* relation to human inflammatory bowel disease. Blumberg merely summarizes which animal models might be better for studying various types of inflammatory bowel disease such as Ulcerative Colitis and Crohn's Disease. However, Blumberg does not suggest or provide motivation, expectation of success or predictability for the particular claimed methods of evaluating efficacy of treatments.

Therefore, the Applicants assert that even if one were to have combined the disclosure of Towaga and Blumberg, one would not have arrived at the Applicants' invention, as claimed. Simply because levels of various cytokines can be measured and various experiments can be run in animal models does not provide the requisite motivation or expectation of success for selecting and measuring particular cytokines and monitoring ratios thereof, in humans, for screening and evaluating the efficacy of a potential treatment. Neither Towaga nor Blumberg provide motivation for methods of screening compositions for efficacy in treating diseases of the bowel in humans.

Therefore, the Applicants assert that the rejection has been overcome. In addition, because Claims 6-8 depend from Claim 1 which the Applicants assert is novel and non-obvious over the cited documents, the Applicants submit that Claims 6-8 are also novel and non-obvious over the cited documents.

New Rejection: Togawa in view of "In vitro production of TNFα, IL-6 and sIL-2R in Chinese Patients with Ulcerative Colitis", Bing, Xia, World J. Gastroenterology 4:252-255. 1998.
Claims 11 and 12 are rejected under 35 USC § 103(a) as being allegedly unpatentable over Togawa as applied to Claim 1 in view of Bing.

The Examiner acknowledges that Towaga does not teach a method of determining efficacy of a treatment of inflammatory diseases of the bowel in mammals wherein the biological sample is peripheral blood nononuclear cells (PMBC) with *in vitro* stimulation,

wherein said *in vitro* stimulation is stimulation with a mitogen. However, the Examiner asserts that Bing discloses assaying production of inflammatory cytokines by PMBCs isolated from patients with IBS stimulated by a mitogen, PHA (phytohemagglutinin). Therefore, the Examiner asserts that it would have been obvious to modify the teachings of Towaga and substitute measurement of the anti- and pro-inflammatory cytokines in mitogen-stimulated PMBCs, for the measurements of Towaga, and such would be equivalent to 'before and after' measurements in humans. The Examiner asserts that one would have been motivated to make such substitution because it would be simpler and less invasive to obtain PMBCs from blood samples versus biopsies from colon tissue, and that once measurement of cytokines were made, calculation of ratios would be an obvious way of monitoring changes in the balance of anti-and pro-inflammatory cytokines. The Examiner asserts that one would have expected success because measuring levels of cytokines in cell culture supernatants is taught by Bing.

The Applicants respectfully traverse the rejection. As argued above, the Applicants maintain that Towaga does not suggest establishing or analyzing any ratios of cytokines, nor particularly the claimed ratios, and that one of skill in the art would not have been led by Towaga's rat study to perform a completely different human study. Bing studied stimulated release of various cytokines by PMBCs in patients with UC (ulcerative colitis) compared to healthy controls, and suggested possible reasons for the results, including active disease state, genetic heritage, and medication. Bing looked for correlation between TNF-alpha, IL-6 and sIL-2r production and disease activity, disease location and medication. However, Bing does not suggest or provide motivation, expectation of success or predictability for the particular claimed methods of measuring particular cytokines, measuring cytokine levels in the same subject (versus subjects and controls as in Bing) before and after treatment, and using particular ratios of cytokines in methods of evaluating efficacy of potential treatments. Neither Towaga nor Bing provide the requisite motivation for the Applicants' particular methods. Simply because one *can* measure cytokines, cytokine levels have been measured in various studies, and one *could* in theory calculate various ratios of cytokines, would not have led one of skill in the art to the present invention. The cited documents do not suggest using particular cytokines to screen potential treatments for inflammatory diseases of the bowel, nor provide

motivation or expectation of success for developing a screening method for evaluating potential treatments for inflammatory diseases of the bowel.

Therefore, the Applicants assert that the rejection has been overcome. In addition, because Claims 11 and 12 depend from Claim 1 which the Applicants assert is novel and non-obvious over the cited documents, the Applicants submit that Claims 11 and 12 are also novel and non-obvious over the cited documents.

Based on the arguments above, the Applicants assert that the rejections have been overcome and respectfully request withdrawal of the rejections.

Conclusion

This response represents an earnest effort to place the application in proper form and to distinguish the invention as now claimed from the applied documents. In view of the foregoing, reconsideration of this application, entry of the amendments presented herein, withdrawal of the rejections, and allowance of all pending Claims is respectfully requested. Early and favorable action in the case is respectfully requested. If the Examiner desires to speak with the Applicants' attorney, the Examiner is invited to please contact the undersigned.

Respectfully submitted,

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